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Abatacept Population Pharmacokinetics and Exposure-Response Analyses for Dose Recommendation of SC and IV Abatacept in Patients With Psoriatic Arthritis

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Introduction

- Both subcutaneous (SC) and intravenous (IV) abatacept, a selective T-cell co-stimulation modulator, are approved for the treatment of adults with moderately to severely active rheumatoid arthritis (RA) and pediatric patients with moderately to severely active polyarticular-course juvenile idiopathic arthritis (pJIA).[1]
- Abatacept has a mechanism of action that is fundamentally different from that of other biologic disease-modifying antirheumatic drugs (bDMARDs), and has proven efficacy and a good safety profile in psoriatic arthritis (PsA).[2,3]
- The exposure–response (E–R) relationship established in RA and pJIA has demonstrated that a steady-state trough concentration (C_{minss}) threshold of 10 µg/mL provides a near-maximal efficacy response.[4]
- For PsA, abatacept is approved as either weight-tiered IV (~10 mg/kg/month) or fixed-dose SC (125 mg/week) treatment:
  - in the US, for the treatment of adults with active disease[1]
  - in the EU, either alone or in combination with methotrexate (MTX), for the treatment of active PsA in adult patients when response to previous DMARD therapy including MTX has been inadequate, and for whom additional systemic therapy for psoriatic skin lesions is not required.[5]

Objective

- Population pharmacokinetic (PPK) and efficacy E–R analyses of abatacept were conducted, in support of the regulatory submission/approval process, to determine whether the proposed IV and SC dosing regimens provided near-maximal efficacy and were therapeutically equivalent in patients with PsA.

Methods

- Combined data from studies with IV or SC abatacept were analyzed to assess clinically relevant exposure outcome measures applicable to both formulations.
- The PPK model was developed with data from 13 Phase II/III studies in RA (11 studies [IV/SC]) and PsA (2 studies [IV/SC]).
- The E–R model of 20% improvement in American College of Rheumatology response criteria (ACR20) at Day 169 was characterized with data from two PsA (IV/SC) studies by a logistic regression model (n=592).
- The effects of the following covariates on the PPK and E–R relationship were examined.
  - PPK analysis
    - Continuous variables at baseline: age, body weight, albumin, calculated glomerular filtration rate (cGFR) and swollen joint count.
    - Categorical variables: disease type (PsA vs RA), sex (male vs female), formulation (SC vs IV), and non-steroidal anti-inflammatory drug use (NSAID; yes vs no).
  - E–R analysis
    - Continuous variables at baseline: age, body weight, tender joint count, swollen joint count, C-reactive protein (CRP), Physician Global Assessment, psoriasis-affected body surface area, Disease Activity Score 28 (DAS28 [CRP]) and disease duration.
    - Categorical variables: sex (male vs female), race (white vs non-white), formulation (SC vs IV), MTX use (yes vs no), corticosteroid use (yes vs no), NSAID use (yes vs no), tumor necrosis factor inhibitor use (yes vs no) and immunogenicity (anti-drug antibody; yes vs no).
- Exposures evaluated in E–R analysis were: steady-state peak (C_{maxss}), trough (C_{minss}) and average (C_{avgss}) concentrations.
- Stochastic simulations were performed to bridge efficacy by comparing IV (~10 mg/kg/month) and SC (125 mg/week) dosing.
  - Using 2000 virtual patients with PsA administered abatacept 125 mg SC weekly, 3 mg/kg IV monthly or ~10 mg/kg IV monthly for 6 months, the expected distributions of abatacept exposure measures and the probability of ACR20 response were simulated using the final PPK and E–R models.
- Model evaluation was conducted by visual predictive check (VPC) methods.

Results

PPK analysis

- The PPK model for abatacept was developed and evaluated using abatacept concentration data from 2737 patients, 493 with PsA and 2244 with RA.
- As seen in RA, abatacept PK was characterized by a linear 2-compartment model with either zero-order IV infusion or first-order SC absorption, and first-order elimination (Table 1). The PK of abatacept was similar in RA and PsA patients.
- Baseline body weight was the only significant covariate considered to have a clinically relevant effect on abatacept exposure (Figure 1).
  - All other covariates were contained within the 80–125% range and therefore not considered to be clinically relevant.
  - The inclusion of the disease effect on clearance resulted in an 8% decrease in clearance for patients with PsA compared with patients with RA. Although statistically significant, this covariate-parameter was not considered to be clinically meaningful.
- Model evaluation, performed by prediction-corrected VPC, showed that most of the observed abatacept serum concentrations fell within the 90% prediction interval, indicating that the final PPK model adequately described abatacept concentration–time profiles (Figure 2).

Table 1. Parameter Estimates of the Final PPK Model

Parameter (units)	Final parameter estimate		IIV/residual variability*	
	Estimate	%RSE	Estimate	%RSE
CL (L/h)†	0.020	2.4	0.094	6.2
Power of body weight on CL	0.65	4.5		
Power of cGFR on CL	0.15	16		
Exponent of sex on CL	–0.057	25		
Power of albumin on CL	–0.67	12		
Exponent of NSAID on CL	0.057	25		
Exponent of SJC on CL	0.080	13		
Power of age on CL	–0.18	14		
Exponent of disease on CL	–0.080	25		
VC (L)†	3.2	1.5	0.067	16
Power of body weight on VC	0.44	12		
Q (L/h)	0.025	13	0.430	33
VP (L)†	4.0	5.3	0.360	16
Power of body weight on VP	0.48	17		
KA (L/h)	0.0025	27	1.90	42
F1‡,‡	1.3	9.4	0.630	17
Additive effect of P2 SC formulation on F1	–1.1	14		
Cov(IIV in VC, IIV in CL)§	NA	NA	0.044	21
Cov(IIV in Q, IIV in CL)§			0.092	31
Cov(IIV in Q, IIV in VC)§			0.059	60
Cov(IIV in VP, IIV in CL)§			0.085	19
Cov(IIV in VP, IIV in VC)§			0.072	27
Cov(IIV in VP, IIV in Q)§			0.28	31
Proportional residual error			0.056	3.8
Additive residual error			0.15	71
Minimum value of the objective function=69455.077				

*ETA Shrinkage: ETA CL: 19.6%, ETA VC: 49.6%, ETA Q: 60.7%, ETA VP: 48.9%, ETA KA: 83.0%, ETA F1: 55.3%; Epsilon Shrinkage Proportional: 14.3%, Additive: 13.8%

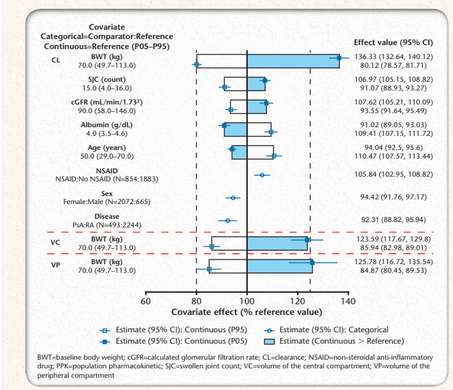
†Covariate effects were estimated relative to a reference 50-year-old patient with RA who is male, weighs 70 kg, has a cGFR of 90 mL/min.1.73 m^2, a baseline albumin level of 4.0 g/dL, SJC of 16, is not on NSAIDs, and was administered the Phase III SC formulation

‡Typical value for F1 is not the absolute bioavailability, $F_{absolute}=1/(1+\exp(-F1-F_{20}))$. At the reference value $F_{absolute}$=78.6%

§The calculated correlation coefficients (r^2) of the off-diagonal omegas were as follows: 0.32 for cov(IIV in VC, IIV in CL), 0.21 for cov(IIV in Q, IIV in CL), 0.12 for cov(IIV in Q, IIV in VC), 0.21 for cov(IIV in VP, IIV in CL), 0.22 for cov(IIV in VP, IIV in VC), 0.51 for cov(IIV in VP, IIV in Q)

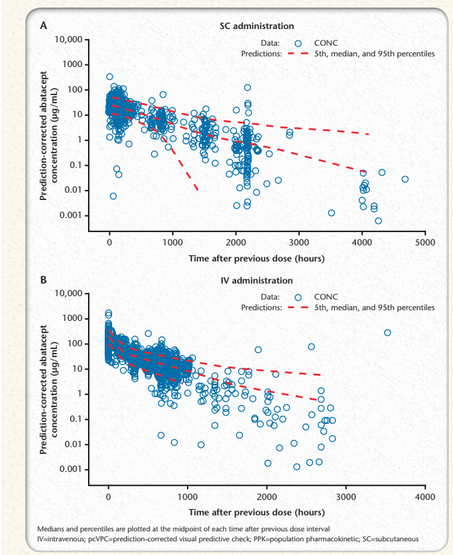
cGFR=calculated glomerular filtration rate; CL=clearance; cov=covariate; F1=bioavailability of SC formulation; IIV=inter-individual variability; KA=absorption rate constant; NA=not applicable; NSAID=non-steroidal anti-inflammatory drug; P2=Phase II; PPK=population pharmacokinetic; Q=inter-compartmental CL; RA=rheumatoid arthritis; RSE=relative standard error; SC=subcutaneous; SJC=swollen joint count; VC=volume of the central compartment; VP=volume of the peripheral compartment

Figure 1. Covariate Effect Forest Plot Based on the Final PPK Model



BWT=baseline body weight; cGFR=calculated glomerular filtration rate; CL=clearance; NSAID=non-steroidal anti-inflammatory drug; PPK=population pharmacokinetic; SJC=swollen joint count; VC=volume of the central compartment; VP=volume of the peripheral compartment

Figure 2. pcVPC of Concentration Versus Time After Previous Dose, by Route (Final PPK Model)



Medians and percentiles are plotted at the midpoint of each time after previous dose interval

IV=intravenous; pcVPC=prediction-corrected visual predictive check; PPK=population pharmacokinetic; SC=subcutaneous

E–R analysis

- As in RA, an E_{max} model (maximum response in logit for C_{minss}) adequately described the E–R relationship for ACR20 in PsA.
- The final E–R ACR20 model parameter estimates are shown in Table 2.
- When comparing across measures of exposure, C_{minss} was considered to be the best predictor of ACR20 response compared to C_{maxss} and C_{avgss}. The probability of ACR20 response at Day 169 increased with increasing values of C_{minss}.
- C_{minss} concentrations equal to or greater than 10 µg/mL were associated with near-maximal ACR20 response.
- There was good agreement between the model-predicted probability of ACR20 response and the observed ACR20 response rate across the range of C_{minss} (Figure 3).
  - MTX use was a statistically significant predictor of ACR20.
    - The probability of ACR20 response on Day 169 increased with use of MTX by ~55% at the median C_{minss} associated with the 10 mg/kg IV monthly regimen (26 µg/mL) and the 125 mg SC weekly regimen (26 µg/mL).
    - However, when the ACR20 responses relative to placebo were compared, MTX did not affect the ACR20 E–R relationship. The improvement in ACR20 response was similar regardless of MTX use.

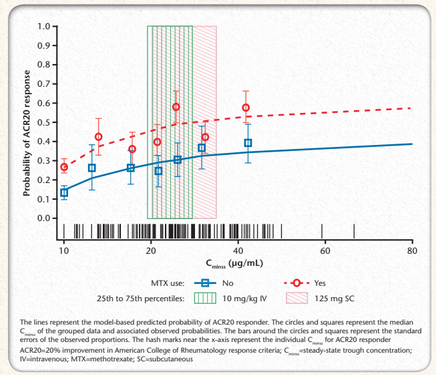
Table 2. Exposure–Response Model for the Probability of ACR20 Response on Day 169

Parameter (units)	Final parameter estimate	
	Typical value	%SEM
Intercept of logit for all patients	–0.987	16.5
Maximum response in logit for C_{minss}*	1.60	52.9
Abatacept C_{minss} producing 50% of E_{max} in logit (µg/mL)*	19.0	133
Additive shift for no MTX use	–0.748	25.7
Minimum value of the objective function=703.995		

*Parameters found to be highly correlated (r^2>0.810)

C_{minss}=trough concentration at steady state; E_{max}=maximum response in logit for C_{minss}; MTX=methotrexate; r^2=correlation coefficient; SEM=standard error of the mean

Figure 3. Model-Predicted Probability of ACR20 Response at Day 169 Versus C_{minss} by MTX use



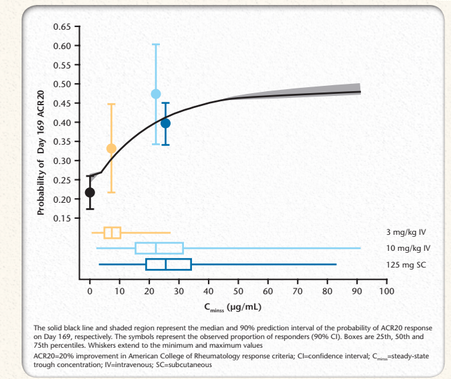
The lines represent the model-based predicted probability of ACR20 responder. The circles and squares represent the median C_{minss} of the grouped data and associated observed probabilities. The bars around the circles and squares represent the standard errors of the observed proportions. The hash marks near the x-axis represent the individual C_{minss} for ACR20 responder

ACR20=20% improvement in American College of Rheumatology response criteria; C_{minss}=steady-state trough concentration; IV=intravenous; MTX=methotrexate; SC=subcutaneous

Stochastic simulations

- While the IV and SC routes of administration have different PK profiles, C_{minss} was similar following administration of weight-tiered IV abatacept (~10 mg/kg IV monthly) and fixed-dose 125 mg SC weekly abatacept regimens. For both regimens, C_{minss} exceeded 10 µg/mL in 95% of patients with PsA across body weights.
- The simulated probability of ACR20 showed that 125 mg SC weekly dosing provides a similar response to 10 mg/kg IV once-monthly dosing. Both dose regimens showed improvements over the 3 mg/kg IV once-monthly regimen (Figure 4).

Figure 4. Observed and Simulated Probability of ACR20 Versus C_{minss} With 90% Prediction Intervals Represented by Shaded Regions and Box Plots of Simulated C_{minss}



The solid black line and shaded region represent the median and 90% prediction interval of the probability of ACR20 response on Day 169, respectively. The symbols represent the observed proportion of responders (90% CI). Boxes are 25th, 50th and 75th percentiles. Whiskers extend to the minimum and maximum values

ACR20=20% improvement in American College of Rheumatology response criteria; CI=confidence interval; C_{minss}=steady-state trough concentration; IV=intravenous; SC=subcutaneous

Conclusions

- The PPK and E–R analyses demonstrate that the abatacept dosing regimens for SC (125 mg/week) and IV (weight-tiered dose approximating 10 mg/kg/month) formulations deliver similar C_{minss} and near-maximal ACR20 responses in patients with PsA.
- As a result, the two formulations and their associated dosing regimens are deemed to be therapeutically equivalent for the treatment of PsA.

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Disclosures

XL, BM, and IGG are employees of and hold stock options and/or bond holdings in Bristol-Myers Squibb. JAP and DM are employees of and hold stock options and/or bond holdings in Cognigen Corporation, a Simulations Plus Company, Buffalo, New York, USA.